BIOMATERIALS FOR MEDICINE

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BIOCERAMICS BASED ON CALCIUM ORTHOPHOSPHATES (REVIEW)

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The modern level of knowledge on biomaterials and bioceramics based on calcium orthophosphates is shown. These chemical compounds have special value, since they are the inorganic component of normal and pathological solid tissues in man and mammals. As a result of the high chemical similarity to the solid tissues of mammals, many calcium orthophosphates possess exceptional biocompatibility and bioactivity. These properties of the material are actively being used for developing artificial bone implants.

Biomaterials are synthetic or natural materials which are either used for replacing individual parts of live organisms or are intended to function in close contact with tissues of live organisms for the purpose of performing an examination, treatment, improvement or replacement of individual tissues, entire organs or some functions performed by them [1]. It is important to draw a clear boundary between biomaterials and biological materials. The former are materials which are friendly to live tissues and therefore can be used for implantation, while the latter are any materials produced by live organisms (for example, wood, cotton, seashells, and so forth). Bioceramics are biomaterials of a ceramic nature.

In mammals calcium orthophosphates are the main inorganic component of normal (teeth, bones, antlers) and pathological (dental and kidney stones, arterosclerotic deposits, and so forth) solid tissues. With the exception of individual parts of the inner ear, all solid tissues in the human body consist of calcium orthophosphates in the form of fine-crystalline, non-stoichiometric, Na-, Mg-, and carbonate-containing hydroxyapatite (so-called biological apatite) [2]. Aside from calcium orthophosphates, which comprise 50 – 60 wt.% of bones, other main components of bones are collagens (30 – 40 wt.%) and water (up to 10 wt.%).

Equilibrium in the three-component system $Ca(OH)_2 – H_3PO_4 – H_2O$ has been examined in detail in the literature [3, 4]. This system contains 11 non-ion-substituted calcium orthophosphates with ion ratio Ca : P = 0.5 – 2.0. The most important parameters of calcium orthophosphates are the ion ratio Ca : P, acidity – alkalinity, and solubility in water. All these parameters are strongly related with the pH of water solutions. The lower the ion ratio Ca : P in calcium orthophosphates, the more acidic and the more soluble the chosen calcium orthophosphate is [2, 4]. A brief list of the characteristics and the standard abbreviations of all existing calcium orthophosphates are presented in Table 1.

Biomaterials and Bioceramic Based on Calcium Orthophosphates. The use of calcium orthophosphates as biomaterials and bioceramics is based on their chemical similarity to the inorganic components of bones and teeth. According to the published data, the first attempt to use a bioceramic made of calcium orthophosphates (this was TCP) as a material for treating artificially produced defects in rabbits was made in 1920 [5]. Unfortunately, today attempts to prepare an artificial bone material suitable for clinical use and possessing good physiological adaptability, biocompatibility, and stability over a long period of time have been only relatively successful. This is clearly demonstrated by the superiority and complexity of the structures created by nature [6].

All biomaterials fall into four groups according to the type of reaction to tissues and organs of live organisms: bioinert, biotolerant, bioactive, and bioresorptive [1, 7]. Bioinert (for example, ZrO_2, Al_2O_3, C, and TiO_2) and biotolerant (for example, polymethylmethacrylate, titanium and cobalt – chromium alloys) materials always produce a physiological response in the form of the formation of a fibrous capsule, which isolates these materials from contact with live tissues. Calcium orthophosphates (chemically pure and containing ionic substitutes) are bioactive and bioresorptive materials. Bioactive materials dissolve somewhat

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TABLE 1.

Ion ratio Ca : P	Calcium orthophosphate [2, 4]	Chemical formula	Solubility, $-\log(K_s)$, at temperature 25°C	Solubility, $-\log(K_s)$, at temperature 37°C	pH range for stability in water solutions at temperature 25°C
	Monocalcium phosphate:				
0.5	monohydrate (MCPM)	$Ca(H_2PO_4)_2 \cdot H_2O$	1.14	No found	0.0 – 2.0
0.5	anhydride (MCPA)	$Ca(H_2PO_4)_2$	1.14	Same	Unstable*
	Dicalcium phosphate:				
1.0	dehydrate (DCPD), mineral brushite	$CaHPO_4 \cdot 2H_2O$	6.59	6.63	2.0 – 6.0
1.0	anhydride (DCPA), mineral monetite	$CaHPO_4$	6.90	7.02	Unstable*
1.33	Octacalcium phosphate (OCP)	$Ca_8(HPO_4)_2(PO_4)_4 \cdot 5H_2O$	96.6	95.9	5.5 – 7.0
1.5	α-tricalcium phosphate (α-TCP)	$\alpha\text{-}Ca_3(PO_4)_2$	25.5	25.5	No data**
1.5	β-tricalcium phosphate (β-TCP)	$\beta\text{-}Ca_3(PO_4)_2$	28.9	29.5	Same**
1.2 – 2.2	Amorphous calcium phosphate (ACP)	$Ca_xH_y(PO_4)_z \cdot nH_2O$ (n = 3.0 – 4.5, 15 – 20 % H_2O)	No data***		~ 5 – 12****
1.5 – 1.67	Calcium-deficient hydroxyapatite (CDHA)	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ ($0 < x < 1$)	~ 85.1	~ 85.1	6.5 – 9.5
1.67	Hydroxyapatite (HA or HAP)	$Ca_{10}(PO_4)_6(OH)_2$	116.8	117.2	9.5 – 12
1.67	Fluorapatite (FA or FAP)	$Ca_{10}(PO_4)_6F_2$	120.0	119.2	7 – 12
2.0	Tetracalcium phosphate (TTKP or tetcp), mineral hilgenstokite	$Ca_4(PO_4)_2O$	38 – 44	37 – 42	No data**

* Stable at temperatures above 100°C.

** Data on calcium orthophosphates cannot be obtained by crystallization from water solutions.

*** Not amenable to accurate measurements. The comparative solubility in an acidic buffer decreases in the following order: ACP > α-TCP > β-TCP > CDHA > HA > FA.

**** Always metastable.

and thereby promote the formation of a layer of biological apatite, which results in the appearance of chemical bonds between an implant and live bone. After adapting to bones, such implants can withstand mechanical loads. Bioresorptive materials gradually dissolve after implantation and make it possible for the newly formed tissues of a live organism to grow into any surface nonuniformities [1, 7].

Bioceramic made from nonporous HA is a good example of a bioactive material, while porous bioceramic, consisting of two-phase calcium orthophosphates (i.e., composites β-TCP + HA or α-TCP + HA) or CDHA or ACP, is an example of a bioresorptive material. Unfortunately, bioceramic made from calcium orthophosphates possesses poor mechanical properties (high brittleness), which makes it impossible to use this material in locations subjected to mechanical loads. Consequently, the medical use of bioceramic based on calcium orthophosphates is limited only to implants which are not subjected to mechanical loads. Examples are individual bones for surgery of the inner ear, filling bone defects in dental or orthopedic surgery, and coating dental implants and metal prostheses [6].

Biomaterials and bioceramic made of calcium orthophosphates are produced in different forms: granules, blocks (dense or porous), injectable compositions, self-hardening cements, coatings on metallic implants, composites from polymers, and so forth [8]. The porous surface of bioceramic gives a large contact surface area between the biomaterial and the growing bone, which results in the formation of a large number of chemical bonds. It has been established that porous HA can be populated with bone tissue. Consequently, manufacturers strive to make bioceramic macroporous (pore size > 100 μm) by adding pore-forming agents, which are either volatile or easily soluble compounds (for example, naphthalene, saccharose, $NaHCO_3$, NaCl, gelatin, microspheres made of polymethylmethacrylate). To facilitate isostatic pressing of cylindrical samples of bioceramic under pressure 200 MPa it is recommended that calcium orthophosphate powder first be premoistened by adding polyvinyl alcohol. Since increasing the size of macropores in a bioceramic (samples with 150, 260, 510, and 1220 μm pores were investigated) did not improve the adaptability of the implants, there is no special need to produce bioceramic with very large pores. Besides macropores, any ceramic also con-

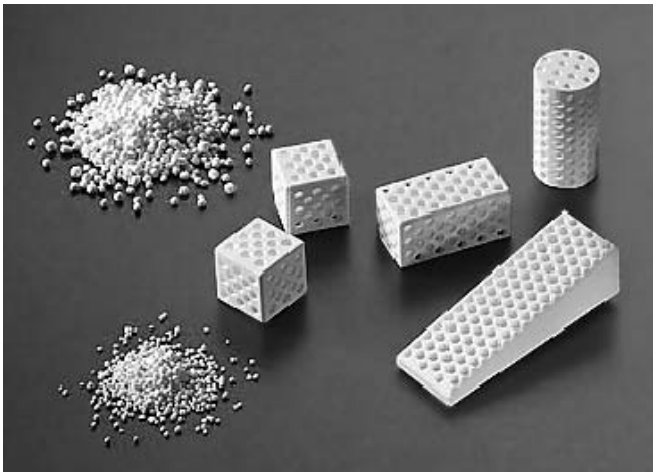

Fig. 1. Bioceramic articles made of calcium orthophosphates.

tains micropores (< 10 μm pore size), which form when the powders are calcined. The sizes of the micropores depend on the calcination conditions (temperature and duration of the process) [9].

In the production of bioceramic with prescribed properties, the calcination and fritting stages are very important. The following intercoupled processes occur during heat treatment of calcium orthophosphates:

removal of all moisture, carbonates, and other volatile compounds (ammonium salts, nitrates, any organic compounds), which entered the calcium orthophosphates during chemical synthesis; removal of all volatile compounds results in the compaction of the ceramic and increases its density;

crystal growth and reduction of the specific surface area;

chemical decomposition of all acidic orthophosphates and their conversion into other phosphates (for example, $2HPO_4^{2-} \rightarrow P_2O_7^{4-} + H_2O$) [2, 4, 9].

It has now been established that increasing the specific surface area and the porosity of bioceramic has a positive effect on the kinetics of the formation of bone and therefore improves bioactivity (the complex of properties of a material that permits creating a strong direct contact with live bone [10, 11]). To understand the relationship between the structure and bioactivity and to design better implants, it is very important to control accurately the total porosity, pore size, and internal porous structure of a bioceramic [10, 11].

Bioceramic based on calcium orthophosphates has now undergone clinical testing in many areas of stomatology and orthopedics. Implants (porous and nonporous) are used for growing alveolar appendages in the jaw, special replacement of teeth, and maxillary-facial surgery. Other areas of application include growing small hearing bones, connecting vertebrae, and treating bone defects [2, 10, 11]. Today, a large number of different types of bioceramics made of calcium orthophosphates exist in the market. For example, the results of physical-chemical investigations of 14 bone-replacing materials made a calcium orthophosphates compared with similar properties of bone tissue are presented in [12]. Commercial and industrial grades of the most important samples of bioceramics based on calcium orthophosphates can be found in the literature [12].

Chemically, bioceramic made up of calcium orthophosphates most often consists of HA, β-TCP, or two-phase calcium phosphate (i.e., solid composite HA and α- or β-TCP) [2, 4, 9]. The most general requirements for an ideal bone implant are: pore size of the order of 100 mm, the biodegradation rate should correspond to the formation rate of new bone (i.e., from several months to two years), hydrophilicity, and the required mechanical strength. Compared with α- and β-TCP, HA is a more stable phase. This is explained by its lower solubility and lower rate of resorption. Since implants made of sintered HA are present in the bodies of live organisms even many years after implantation, bioceramic based on α-TCP and β-TCP or two-phase calcium phosphate is preferable for medical purposes [2, 4, 9 – 11]. On the basis of the results of investigations, different calcium orthophosphates have been arranged in order of decreasing bone-formation indices: two-phase calcium phosphate synthesized at low temperatures (rough or smooth surface), ≈ two-phase calcium phosphate synthesized at intermediate-range temperatures, ≈ TCP > unsintered HA > two-phase calcium phosphate calcined at high temperatures (with rough or smooth surface), > HA calcined at high temperatures. Samples of calcium orthophosphate bioceramic existing on the market are displayed in Fig. 1.

Another concept for treating damaged bones appeared after the invention of hydraulic bone cements made from calcium orthophosphates which solidify inside bone defects [13, 14]. As a result, a low-temperature of bioceramic is formed. On the basis of phase composition, all bone cements are divided into two large groups. Cements consisting of a dry mixture of powders of two different calcium orthophosphates (acidic and alkaline) comprise the first group. These cements solidify with the addition of water by chemical interaction between the base and acid. Segments where the initial and final calcium orthophosphates have the same ion ratio Ca : P comprise the second group. A typical example of cements in the first group is a mixture of DCPD and TTCP, and a typical example of a cement belonging to the second group are cements from ACP or α-TCP; the latter cements hydrolyze into CDHA on contact with water solutions [13, 14].

Cements in both groups solidify on contact with water. When mixed with water, power from the initial calcium orthophosphate(s) dissolves and then the less soluble calcium orthophosphates crystallize. This results in disordered growth of new crystals, which, entwining into a tight ball, form a bioceramic monolith, which gives the cement mechanical strength. It has been established that bone cements solidify within the first 6 h. By this time approximately 80% of the initial calcium orthophosphates transforms into the fi-

TABLE 2.

Method	Coating thickness, μm	Advantages	Disadvantages
Thermal sputtering	30 – 200	High deposition rate, low cost	Monitoring done by observation, high temperatures cause decomposition, fast cooling results in amorphization
Spraying	0.5 – 3.0	Uniform coating thickness on flat substrates, dense coatings	Monitoring done by observation, expensive, requires a long period of time, amorphous coatings
Deposition by pulsed laser	0.05 – 5	Permits covering with crystalline and amorphous phases, form dense and porous coatings	Monitoring done by observation
Dynamic mixing method	0.05 – 1.3	High adhesion	Monitoring done by observation, expensive, amorphous coatings
Deposition by dipping	0.05 – 0.50*	Cheap, fast, permits covering substrates with a complex composition	High-temperature calcination necessary, mismatch of thermal expansion
Deposition from a colloidal solution	< 1	Permits covering substrates with a complicated shape, room temperature, relatively cheap since the coatings are thin	Monitoring of the atmosphere is required in some cases, expensive initial materials
Eectrophoresis	0.1 – 2.0*	Uniform coating thickness, high deposition rate, permits covering substrates with a complex composition	Difficult to obtain crack-free coatings, high-temperature calcination required
Bioimitation method	< 30	Room temperature, biological apatite forms, permits covering substrates with a complex shape, biomedical hormones can be introduced	A long period of time is required, solutions must be renewed, and the pH must be strictly maintained constant
Hot isostatic press	0.2 – 2.0	Dense coatings	Substrates with complex composition cannot be coated, high temperature, mismatch of thermal expansion, differences in elasticity, expensive, removal of encapsulated material

* Indicated in millimeters.

nal product, and the compression strength is already 40 – 60 MPa. The solidification rates of cements can be easily controlled by adding other chemical reagents and by the quantity of water added. Even though there is a great diversity of the initial formulas, cements based on calcium orthophosphates can form only three final products: CDHA, DCPD, and ACP [13, 14].

Hydraulic cements made from calcium orthophosphates possess unique properties which facilitate their application in surgery. These cements our biocompatible, bioactive, and biodecomposable. Since the structure and chemical compositions of such cements are close to the analogous properties of the inorganic phase of bone tissue, the inorganic components of the cements are well assimilated by bone-forming cells and are used by them for healing bone defects [13, 14]. Unfortunately, calcium orthophosphates cements possess low mechanical strength, but this property can be improved by adding polymers. The main advantage of hydraulic cements is good adaptability to the complex geometry of any bone defects. Injectable macroporous bone cements made of calcium orthophosphates have been invented very recently. Additional ways to improve hydraulic bone cements is to add live cultures of bone-forming cells to them.

Bioceramic coatings made of calcium orthophosphates deposited on the surface of implanted metals are also widely used in medicine [15, 16]. Metallic implants are used in fitting endoprostheses (complete hip replacement) and for strengthening artificial teeth. Metal implants for such purposes must be used for such purposes because of the strict requirements for mechanical strength.

Since metals cannot form chemical bonds with live bone, researchers are now looking for ways to solve this problem. At the present time the best solution has been found to be coating metals on the outside by a layer of bioceramic based on calcium orthophosphates. In so doing, the metal implant "is responsible" for the mechanical strength of the entire structure; the outer layer of bioceramic provides good adaptability. Possible methods for depositing calcium orthophosphates on a metal surface are presented in Table 2, and the main advantages and disadvantages of each method, including the main properties of the calcium orthophosphate coatings formed, are described in detail in the literature [15, 16]. It has now been determined that bioceramic coatings made of

HA as a system for securing hip joints are serviceable for a short (eight years) and intermediate (17 years) periods of time after implantation.

Bioceramic Based on Calcium Orthophosphates in Tissue Engineering. The three main disadvantages of modern bone implants are:

impossibility of self-restoration;

impossibility of providing for blood flow;

incapability of changing the structure and properties in response to external conditions, such as mechanical loads.

It is obvious that only live bone possesses all of these properties. But bones themselves also nucleate and grow, have a complex hierarchical structure and nonlinear properties, perform numerous functions in the body, and are a biodecomposable organomineral composite material. Ideally, bone-substituting prostheses should possess all of these properties [16].

Tissue engineering is an interdisciplinary field of science and engineering, where a combination of live cells, biomaterials, and required biochemical hormones are used in diverse combinations to improve, replace, restore, maintain, or expand the possibilities of live tissues and even entire organs [17]. This field of science appeared a little more than 10 years ago [18] and is now developing very rapidly because of the following key advantages:

the solutions which it provides are long-term, safer and cheaper compared with any other solutions;

minimal use of donor tissues and organs, which solves the problem of immunological compatibility;

foreign compounds and materials are kept out of live organisms.

Since two of the three main components (live cells and biochemical hormones) of tissue engineering fall far outside the framework of the present review, the subject of tissue engineering is considered only with respect to bioceramics.

Live cells of bone tissue are implanted or sown on an artificial bioceramic structure, called a substrate or matrix, which is capable of supporting the formation of three-dimensional structures. These substrates are the basis for the subsequent growth of bone on them and provide the specific environment and "architecture" for bone growth. Substrates perform at least one of the following functions [19]:

providing a location for attachment and growth of live cells on them;

delivering and retaining cells and hormones;

delivering nutrients and removing waste products;

having a definite mechanical and biological effect on the development of a cell phase.

To achieve restoration of bone tissue, bioceramic substrates must meet definite requirements. Their surface must not be too smooth, otherwise it would be difficult for cells to attach. They must be porous with adequate pore size, so that at the moment of implantation they can be rapidly permeated with blood, which allows for diffusion of cells and nutrients. They must be biodecomposable, since as you bone is formed, these substrates must be gradually dissolve, which will make it unnecessary to remove them surgically [17 – 19]. The dissolution rate of the substrates must be as close as possible to the rate of growth of new bone [7]. For clinical use, important factors are ease and safety of introduction at locations of bone defects.

In the case of bone implants, the goal of tissue engineering is to create bioceramic porous three-dimensional implants from calcium orthophosphates, which are physical and chemical signal markers, which seemingly "guide" the attachment to cells and their growth as well as the construction of a three-dimensional structure of the newly formed bone. To better meet these goals, chemists and materials engineers are considering how to improve further the properties of bioceramics based on calcium orthophosphates. From the standpoint of chemists, this means synthesizing new ion-substituted calcium orthophosphates, while from the standpoint of materials engineers the main directions are nanocrystalline structures, organomineral hybrids, ceramic fibers, microspheres, porous three-dimensional structures made of ACP, HA, and two-phase calcium phosphate, bioceramic with a porosity gradient, as well as hierarchical structures.

The effect of porosity of a bioceramic made of HA on the formation of bone by the method of culturing stem cells from the bone marrow of rats is being studied. The possibility of producing bioceramic substrates with a prescribed structure and properties opens up brilliant prospects for calcium orthophosphates [6].

At the present time the main thrust in the field bioceramics and biomaterials made of calcium orthophosphates is toward synthesis of composites. For example, bioceramic composites of HA with carbon nanotubes have been described very recently [20]. In addition, a great deal of attention is being devoted to improving bone cements, multiphase compositions imitating as much as possible the composition and properties of bone tissue, and development of bioceramic substrates based on calcium orthophosphates for use in tissue engineering.

Another rapidly developing direct action is the study of nanostructured and nanocrystalline materials based on calcium orthophosphates in order to imitate the complex hierarchical structure of bones and teeth [6].

The expected key applications of bioceramics made from calcium orthophosphates in the future are (but not limited to) their use in systems for delivering medicines and as carriers of bioactive proteins, hormones, and live bone-forming cells [21, 22].

In closing, we note that even though research on bioceramics made of calcium orthophosphates has a long history many scientific and technological problems remain unsolved. This is glaringly manifested in the absence of artificial implants on the market which can easily replace damaged or worn bones. For the time being, only relative victories have been won along this path.

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